REMARKS

Claims 1-59 are pending in the above-identified application. Claim 10-32 and 42-59 are presently withdrawn from consideration pursuant to a restriction requirement. Claims 1 and 33 have been amended. Support for the amendments to the claims is found, *inter alia*, throughout the specification as filed. More particularly, support for the amendment to claims 1 and 33 is found, *inter alia*, on page 1, line 12 of the specification. No new matter has been added with the foregoing amendment. As such, Applicants respectfully request reconsideration.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with Markings to Show Changes Made."

The Invention

The present invention provides methods that are useful for identifying therapeutic agents for the treatment of a CAR-mediated disorder or condition. The methods include determining whether the candidate therapeutic agent modulates CAR-mediated intermolecular interactions by determining whether the level of a cholesterol level indicator is modulated in a mammal.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1-9 and 33-40 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. In order to expedite prosecution, claims 1 and 33 have been amended to clarify that the acronym CAR refers to constitutive androstane receptor. As such, Applicants respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejection Under 35 U.S.C. § 103(a)

Claims 1, 3-9 and 33-41 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,710,017 ("Moore *et al.*") in view of

Sueyoshi *et al.*, *Journal of Biological Chemistry* (1999) 274(10):6043-6046 ("Sueyoshi *et al.*"). According to the Office Action, one of skill in the art would have been motivated by the teachings of Moore *et al.* to identify ligands which can modulate a CAR-mediated intermolecular interaction by measuring a cholesterol indicator from the teachings of Sueyoshi *et al.* In response, Applicants respectfully traverse the rejection.

As set forth in M.P.E.P. § 2143:

> [t]o establish a *prima facie* case of obviousness, three basic criteria must be met. *First* there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *Second*, there must be a reasonable expectation of success. *Finally*, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure.
>
> *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991)

All three elements set forth above must be present in order to establish a prima facie case of obviousness. Applicants assert that a *prima facie* case of obviousness has not been established because there is no suggestion or motivation to modify the reference or to combine reference teachings. Furthermore, the combined references do not teach or suggest all the claim limitations.

The present invention relates to, *inter alia*, methods that are useful for identifying therapeutic agents for the treatment of a CAR-mediated disorder or condition. The methods include determining whether the candidate therapeutic agent modulates CAR-mediated intermolecular interactions by determining whether the level of a cholesterol level indicator is modulated in a mammal. Claim 1 reads as follows:

> 1. (Amended) A method for identifying a therapeutic agent for use in treating a constitutive androstane receptor (CAR)-mediated disorder or condition, the method comprising:

identifying a candidate therapeutic agent by screening one or more compounds to determine whether said compounds can modulate a CAR-mediated intermolecular interaction;

administering the candidate therapeutic agent to a test mammal; and

determining whether the level of a cholesterol indicator is modulated in said test mammal.

A key step in claim 1 is the measurement of the level of a cholesterol indicator. A "cholesterol indicator" is defined as a marker of the level of cholesterol present in a cell or a mammal (*see*, page 13, lines 8-9 of the specification).

Moore *et al.* teach a purified DNA encoding a CAR receptor (*see*, Abstract, Moore *et al.*). Moore *et al.* also teach methods of expressing the CAR receptor (*see*, column 13, lines 27-46, Moore *et al.*). The Examiner acknowledges that Moore *et al.* do ***not*** teach determining whether the level of a cholesterol indicator is modulated in the test mammal (*see*, page 4 of the Office Action). The Office Action alleges that motivation for identifying ligands which can modulate a CAR-mediated intermolecular interaction by measuring a cholesterol indicator is provided at column 14, lines 30-40 of Moore *et al.* Although Moore *et al.* teach that the methods of the invention may be used to reduce disorders in any mammal, the use of cholesterol indicators is neither taught nor suggested. Contrary to what is stated in the Office Action, a simple statement that the methods of the invention may be used for reducing disorders does ***not*** provide any motivation for one to modify the methods themselves. At no point do Moore *et al.* teach or suggest determining whether the level of a cholesterol indicator is modulated in a test mammal. Furthermore, Moore *et al.* do not teach or suggest a method comprising identifying a candidate therapeutic agent by screening one or more compounds to determine whether the compounds can modulate a CAR-mediated intermolecular interaction, administering the candidate therapeutic agent to a test mammal, and determining whether the level of a cholesterol indicator is modulated in the test mammal.

Sueyoshi *et al.* teach that the CYP2B6 gene becomes phenobarbital inducible in androstenol-treated HepG2 cells which express CAR. While CYP2B6 is a CAR target gene, it is not a cholesterol indicator. Sueyoshi *et al.* do not teach determining whether the level of a cholesterol indicator is modulated in a test mammal. Sueyoshi *et al.* simply do not teach the use of cholesterol indicators. Moreover, Sueyoshi *et al.* do ***not*** teach or suggest a method comprising identifying a candidate therapeutic agent by screening one or more compounds to determine whether the compounds can modulate a CAR-mediated intermolecular interaction, administering the candidate therapeutic agent to a test mammal, and determining whether the level of a cholesterol indicator is modulated in the test mammal. Therefore, Sueyoshi *et al.* do not remedy the deficiencies of Moore *et al.*

Since no motivation to combine the cited references is provided in either Moore *et al.* or Sueyoshi *et al.*, and the combined references do not teach or suggest all the claim limitations, the present invention is not obvious. As such, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

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